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PATENT

Attorney Docket No.: A-68087-1/RMS/DCF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK CHEE et al.

Serial No.: 09/425,633

Filing Date: October 22, 1999

For: SEQUENCE DETERMINATION OF NUCLEIC ACIDS USING ARRAYS WITH MICROSPHERES

Examiner: Forman, B. J.

Group Art Unit: 1655

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CERTIFICATE OF MAILING

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on May 1, 2002.

Signed: Victoria T. Linne
Victoria T. Linne

Box Fee Amendment
Assistant Commissioner for Patents
Washington, DC 20231

RESPONSE TO OFFICE ACTION

Sir:

This response is submitted with a Request for Continued Examination under C.F.R. 1.114 and a declaration pursuant to C.F.R. § 1.132. This response is accompanied with a petition for a four month extension of time and the appropriate fee, making this a timely response. This response is submitted after a notice of appeal was filed on November 1, 2001. The Assistant Commissioner is hereby authorized to charge any fees, including extension of time fees or other

relief as may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our File A-68087-1/RMS/DCF).

Please enter the following claim amendments and consider the remarks herein.

AMENDMENTS

23. The method according to claim 42, wherein said detectable label comprises a fluorophore.

24. (Amended) The method according to claim 42, wherein said detectable label comprises biotin.

C1

25.(Amended) The method according to claim 42, wherein said detectable label comprises imine-biotin.

26.(Amended) The method according to claim 42, wherein said dNTP comprises a functional group for addition of a fluorophore.

29.(Amended) The method according to claim 42, wherein said substrate is a fiber optic bundle.

C2

30.(Amended) The method according to claim 42, wherein said substrate is selected from the group consisting of glass and plastic.

31.(Amended) The method according to claim 42, wherein said detectable label is a fluorophore.

42. (NEW) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising:

a) providing a hybridization complex comprising

i) a first target sequence comprising

1) a first nucleotide at a detection position; and

2) a first target domain directly 5' adjacent to said detection position;

3) a second target domain 3' adjacent to said detection position;

C3

ii) a first ligation probe hybridized to said first target domain;

iii) a second ligation probe hybridized to said second target domain;

b) contacting said hybridization complex with:

i) an extension enzyme;

ii) at least one dNTP;

such that if the base of said dNTP is perfectly complementary to the base of said detection position, said first ligation probe is extended to form a ligation structure;

c) contacting said ligation structure with a ligase to ligate said first extended ligation probe and said second ligation probe to form a ligation product; and

d) detecting the presence of said ligation product to identify the nucleotide at said detection position, said detecting comprising providing a substrate with a surface comprising discrete sites, further comprising a population of microspheres comprising at least a first and a second subpopulation, wherein each

subpopulation comprises a capture probe, wherein said capture probe hybridizes to a sequence contained within said ligation product.

43.(NEW) The method according to claim 42 wherein one of said ligation probe comprises an adapter sequence that hybridizes to said capture probe.

C3

44.(NEW) The method according to claim 42 wherein said dNTP comprises a detectable label.

45. (NEW) The method according to claim 42 wherein said capture probe attached to a microsphere on a surface of said substrate serves as said first ligation probe.

46
~~47~~.(NEW) The method according to claim 42, wherein said capture probe is a nucleic acid.

Rule 1.126

47
~~48~~.(NEW) The method according to claim 42, wherein said capture probe is a protein.

48
~~49~~.(NEW) The method according to claim 42, wherein said discrete sites are wells.

4a
~~50~~.(NEW) The method according to claim 42, wherein said microspheres are randomly distributed on said substrate.

REMARKS

Claims 23-26, 29-31, 42-50 are pending. Claims 23-26 and 29-31 are amended. Please cancel claims 17-22, 27-28, and 32-41 without disclaimer or prejudice. Support for new claims 42-50 are found throughout the specification as filed, for example at page 7, lines 31-37(figures 10A-10C), p. 40, lines 20-34. Support is found throughout the specification including the figures and the claims. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**" For the Examiner's convenience a clean copy of the currently pending claims is appended hereto as Appendix A. Applicants respectfully request entry of the amendments as they put the claims in form for allowance.

Rejection Under 35 U.S.C. § 112

Applicants note that upon entry of the amendments, the Advisory Action mailed on August 29, 2001 states that the rejections under § 112, second paragraph would be withdrawn. Accordingly, Applicants respectfully request the entry of the above amendments and withdrawal of the 112 rejections.

Response to Rejections Under 35 U.S.C § 103

Claims 17-41 are rejected under 35 U.S.C. § 103 as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, filed August 9, 1996), Walt et al. (U.S.Patent No.6,023,540 filed March 14, 1997) and Lyamichev et al. (Nature Biotechnology, March 1999,17: 292-296). The Examiner notes that the claims are rejected for reasons of record in the previous Office Action,

mailed 24 August 2000 as applied to new claims 17-41 according to Examiner's best understanding of the claims. However, Applicants note that the Office Action mailed 24 August 2000 set forth two rejections under 103. Former claims 1-12 and 15-16 were rejected under 103 as being unpatentable over Nikiforov et al in view of Walt et al. Claims 13-14 were rejected under 103 as being unpatentable over Nikiforov et al in view of Walt et al and further in view of Lyamichev et al. In contrast, it appears that there is only a single current rejection of all of claims 17-41 under 103 as set forth above. Applicants have attempted to interpret the rejection in light of the rejections set forth in the previous Office Action.

Nikiforov et al. is directed to a ligase/polymerase mediated method of detecting a nucleotide at a preselected site by immobilizing a first probe to a solid support that will hybridize to a region of a target sequence, then adding a second probe that will hybridize to a second region of the target whereby the first and second probe are separated by a single nucleotide and then there are two subsequent reactions of extension of one of the ligation probes and then ligation of both probes. Nikiforov does not teach the use of microspheres on the surface of a substrate.

Walt et al. teaches among other things, the use of microspheres comprising nucleic acid capture probes on surfaces to detect the presence or absence of nucleic acid sequences. Walt et al. does not teach the combination of ligation and extension reactions (Genetic Bit Analysis™) or any polymorphism detection reactions.

Lyamichev et al. is directed towards the detection of a nucleotide at a selected site through the formation of a cleavage structure and cleavage structure specific enzymes. Lyamichev et al. does not teach Genetic Bit Analysis™ or the use of microspheres on the surface of a substrate. Further, Applicants would like to point out that since claims 13 and 14 have been

cancelled (the claims upon which the rejections using this reference was based) and none of the pending claims are directed to a cleavage reaction, any rejections based on this reference should be withdrawn.

The Examiner states that it would have been obvious to modify the microsphere-attached oligonucleotides of Nikiforov et al. by arraying the microspheres on the surface of a substrate as taught by Walt et al. for the benefits of economy and uniform signal detection.

The test is not whether one device can be appropriate substitute for another. See *Hybritech Inc. v. Monoclonal Antibodies*, Inc., 802 F. 2d 1367, 1383, 231 USPQ 81, 93 (Fed. Cir. 1986).

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

The methodology of the present invention of detecting nucleotides at specific positions within a target sequence using microspheres attached to a substrate by performing the

combination of extension and ligation reactions in conjunction with microspheres on the surface of a substrate (claim 42) is not suggested by the cited prior art references. Although Nikiforov et al. and Lyamichev et al. are directed to detecting nucleotides at specific positions neither one of them teach the use of microspheres on the surface of a substrate.

Applicants respectfully submit that the Examiner has failed to set forth a prima facie case of obviousness because the teaching or suggestion to make the combination that reaches the claimed invention is not found in the prior art.

Therefore, a prima facie case of obviousness has not been met and the rejections are improper. Applicants respectfully request that the rejection be withdrawn.

In addition to the lack of objective reasons supporting a motivation to combine the references, the evidence submitted herein of the secondary consideration of commercial acquiescence compel a finding of nonobviousness.

The Supreme Court of the United States has stated that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." Graham v. John Deere Co., 148 USPQ 459 (1996).

The Federal Circuit has emphatically and repeatedly held that objective evidence of nonobviousness must be taken into account always and not just when the decision maker is in doubt: "objective evidence such as commercial success, failure of others, long felt need, and unexpected results must be considered before a conclusion on obviousness is reached" (Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986).

Additionally the secondary consideration of commercial acquiescence or licensing is deemed an important consideration in the nonobviousness determination, see In Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc., (Fed. Cir.1992) the patentee's and infringer's major competitor took a license from the patentee. The Federal Circuit noted that "such real world considerations provide a colorful picture of the state of the art, what was known by those in the art, and a solid evidentiary foundation on which to rest a nonobviousness determination." See also Chisum volume 2 §5.05[3] "Acquiescence by a substantial portion of the competitors in a market to the validity of a patent generally through acceptance of a license has been regarded as evidence supporting patentability. The theory behind use of commercial acquiescence is that persons would not usually act in a fashion contrary to their economic interests unless convinced of the patent's validity."

It is important to note that the composition of claims 17-20, 23-31 and claim 42 of the BeadArray™ detection technology for genotyping is encompassed in the in-house servicing agreements as provided below and supported by a declaration pursuant to 37 C.F.R. § 1.132. This establishes a nexus between the commercial agreements and the merits of the claims.

A news release dated June 29, 2001 announced that Illumina signed a commercial agreement with GlaxoSmithKline to provide single nucleotide polymorphism genotyping services (in-house by Illumina) on a sample collection provided by GlaxoSmithKline. Under the terms of the agreement, Illumina will use its BeadArray™ detection technology to "score", or determine the frequency of specified SNPs in the sample set. Applicants point out that GlaxoSmithKline is a global pharmaceutical firm and leader in employing new technologies to accelerate drug discovery and well respected in the industry.

Applicants further point out that GlaxoSmithKline is an economically successful corporation and would not be inclined to enter into a in-house service agreement for the sole purpose of avoiding costly litigation. The fact that GlaxoSmithKline entered into a commercial agreement with Illumina for the purpose of Illumina providing in-house Genotyping services based on the claimed invention is strong support for a finding of nonobviousness based on commercial acquiescence.

A news release dated January 8, 2002 announced that Illumina signed a commercial agreement with John Hopkins Medical University, Institute of Genetic Medicine to provide single nucleotide polymorphism genotyping services on a sample collection provided by the Institute. Under the terms of the agreement, Illumina will use its BeadArray™ detection technology to "score", or determine the frequency of specified SNPs in the sample set. Applicants point out that John Hopkins is a world leader in the research of genetic factors associated with various diseases.

A news release dated January 28, 2002 announced that Illumina signed a commercial agreement with investigators at Boston University Medical Center to provide single nucleotide polymorphism genotyping services for a large scale research project on preterm birth. Applicants point out that Boston University is a highly respected research institution.

A news release dated April 25, 2002 announced that Illumina signed a commercial agreement with the University of California, San Diego to provide single nucleotide polymorphism genotyping services on a sample collection provided by the University's Laboratory of Psychiatric Genomics in order to provide a better understanding of the genetic

basis of bipolar psychiatric disorders. Applicants point out that the University of California, San Diego is a highly respected research institution.

In addtion, Illumina signed an agrrement with Oxagen, a clinical genomics company which uses databases of family studies to identify and validate disease-causing genes (news release of March 19, 2002). In the agreement, Illumina will use its BeadArray™ detection technology to assay single nucleotide polymorphisms provided by Oxagen and generate several million genotype calls from the sample collection. The statement of Oxagen's Chief Executive Officer is germane in regards to the reasons of the commercial agreement with Illumina:

> Illumina's BeadArray™ platform will give us the sample throughput and the accuracy we need to extract maximum information from our valuable samples.

Thus, the advantages of high sample throughput and accuracy provided by the BeadArray™ detection technology for single nucleotide polymorphism genotyping is given as a basis for the commercial agreement rather than other factors such as potential conflicts arising from overlapping technology.

Applicants point out that all of these commercial agreements involve companies or research centers consisting of personnel highly skilled in the art who would not make commercial agreements in a fashion contrary to their economic interests and their acceptance of the service agreements is evidence supporting the patentability of applicant's claimed invention and compel a finding of nonobviousness.

The Applicants respectfully submit that the rejection of claims based on 35 USC §103 obviousness is improper and respectfully requests withdrawal of the rejections.

In conclusion, neither Nikiforov et al. (a); Walt et al.; or Lyamichev et al or their combination teach or suggest the use of microspheres on the surface of a substrate which can be randomly placed for the detection of significantly large numbers of single nucleotide polymorphisms. In addition the strong factual evidence of commercial acquiescence as a secondary consideration of nonobviousness as provided above and within the enclosed declaration provided herewith, necessitate a finding of nonobviousness.

The applicants submit that a *prima facie* case of obviousness has not been established since the secondary considerations of nonobviousness, as mandated by the Federal Circuit, lead to a finding of nonobviousness. In particular the factual evidence supporting a finding of commercial acquiescence as provided above and in the accompanying declaration support a finding of nonobviousness.

Respectfully submitted,

FLEHR, HOHBACH, TEST,

ALBRITTON & HERBERT LLP

Dated: May 1, 2002

Robin M. Silva
Reg. No. 38,304

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
encls:: 37 C.F.R. 1.132 Declaration
Request For Continued Examination

JOHN R. STUELPNAGEL

Illumina, Inc.
9390 Towne Centre Drive, Suite 200
San Diego, CA 92121
858-587-4290, ext 226

P.O. Box 281
Cardiff, CA 92007
760-943-1541

EXPERIENCE

Illumina, Inc. San Diego, CA
VP Business Development and Director *1998-present*
Acting President & CEO *1998-Oct. 1999*
Acting CFO *1998-Apr. 2000*

- Founded Illumina from technology licensed from Tufts University.
- Hired key scientific team, recruited Scientific Advisory Board, set initial product focus, acquired nGenetics, acquired Spyder Instruments, and determined the strategic direction of Company.
- Identified and recruited the permanent President & CEO.
- Raised $38 million in private financing in three venture rounds and participated actively in $100 million IPO.
- Negotiated and closed $15 million joint development program with Applied Biosystems.
- Licensed additional intellectual property and established numerous research collaborations, including those with The Dow Chemical Company and Chevron.
- Guided the development of the intellectual property portfolio to include 15 issued patents and 50+ patent applications.
- Identified and negotiated real estate transactions, including the $36 million purchase of the Company's corporate headquarters.

CW Group Cardiff, CA
Associate *1997-1998*

- Joined CW Group when CW Group acquired Catalyst Partners (see below).
- Responsible for identifying new investment opportunities and working with portfolio companies in business development.
- Founded Illumina for CW Group.
- Assisted the General Partners in raising $100 million venture fund.

Catalyst Partners/Avalon Ventures Cardiff, CA
Principal *1996-1997*

- Identified and researched start-up opportunities in bioinformatics, chip olfaction, proteomics and acceleration of drug development.
- Founded bioinformatics company and negotiated its merger with another bioinformatics company, Pangea Systems. The combined company received $10 million in venture financing.

- Worked with portfolio companies in business development:

Caliper Technologies

- Performed financial analysis and worked on the team that negotiated strategic relationship with Hewlett-Packard valued in excess of $100 million.
- Worked on team that negotiated strategic relationships with Hoffman-LaRoche and Dow Chemical valued in excess of $30 million.
- Led licensing negotiations for key technologies, including the successful renegotiation of its core technology, reducing the royalty rate by 75%.
- Analyzed spin-out business opportunities, including ultra-high throughput drug screening and pharmacogenetics.

IDUN Pharmaceuticals

- Licensed key technologies.

InnoCal, Venture Capital — Costa Mesa, CA
Intern — *Summer, 1996*

- Researched the health care information industry to identify investment opportunities.
- Evaluated combinatorial chemistry companies in support of an acquisition offer.
- Analyzed the veterinary market for a portfolio company developing a human pharmaceutical.

Keystone Biomedical, Inc. — Los Angeles, CA
Consultant — *1995-1996*

- Assisted in the founding of biotechnology.
- Authored business plan used in obtaining $1.2 million in seed capital.

Veterinary Practice — Santa Barbara and Santa Ynez, CA
Veterinarian — *1983-1996*

EDUCATION

M.B.A., The Anderson School at UCLA — *1997*

Awards and Honors

Henry Ford II Fellowship to top student
Edward W. Carter Fellowship to top 2% of class
Venture Fellowship
Dean's Fellowship
Director, Entrepreneurs Association

D.V.M., School of Veterinary Medicine, UC Davis — *1983*

Awards and Honors

Valedictorian, School Medalist

University of California Regents Scholar
CVMA Award for Practice Excellence
Merck Award
Phi Zeta Honor Society, President

B.S., College of Agriculture, UC Davis *1979*

Awards and Honors

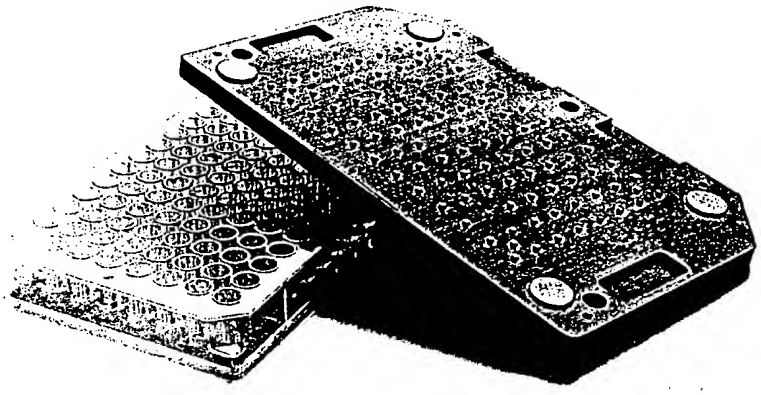
Valedictorian, College Medalist

Research

Etiology, Biochemistry and Diagnosis of Degenerative Joint Disease

Illumina's SNP Genotyping Services and Technology

How Illumina's BeadArray™ platform and an advanced LIMS environment provide high throughput, accuracy and low genotyping cost.



Illumina's 96-bundle Array of Arrays enables parallel processing of nearly 200,000 SNPs.

INTRODUCTION

Illumina has developed SNP genotyping services that leverage highly multiplexed and automated assays processed on our BeadArray™ platform. Illumina's system delivers superior performance, throughput, cost-effectiveness and accuracy to researchers interested in large-scale genotyping.

With a capacity approaching one million genotypes per day, Illumina's scientific operation integrates a high degree of automation with an advanced laboratory information management system (LIMS) for error-free sample tracking.

Illumina's high throughput genotyping services will enable linkage analysis, fine mapping of selected chromosomal regions, identification of candidate gene SNPs, and large association studies.

GENOTYPING SERVICES MENU

- **Custom assay development and genotyping**
- **SNPs in Drug Metabolizing Enzymes (≥ 175 ADME-changing loci)**
- **Linkage Sets (targeted delivery Q4 '01)**
- **Disequilibrium Set (targeted delivery Q2 '02)**

BEADARRAY™ TECHNOLOGY

At the heart of Illumina's platform is our BeadArray technology—a fiber optic-based array system that allows miniaturized, very-high-throughput genetic analysis.

In our current implementation, fiber bundles are manufactured to contain nearly 50,000 individual, light-transmitting fiber strands. We convert each fiber bundle into an array by first chemically etching a microscopic well at the end of each fiber strand within a bundle. This process creates up to 50,000 discrete microscopic wells per bundle.

In a separate process, we create sensors by affixing a specific type of molecule to beads, each bead approximately 3-microns in diameter, in high quality-controlled batches. The particular molecules on a bead define that bead's function as a sensor. For example, we create a batch of SNP sensors by attaching a particular DNA sequence to each bead in a batch. We then combine these batches of coated beads to form a pool specific to the type of array we intend to create. In the case of our SNP genotyping product, the array pool we have selected uses DNA sequences that do not cross-hybridize with themselves or with known genomic DNA

The next step in the manufacturing process involves creating the self-assembled array. By dipping the bundles into a pre-mixed bead pool the coated beads self-assemble individually, one bead per well, on the end of each fiber in the bundle to create the array. In our SNP genotyping array, the bead pool consists of up to 2000 unique sequences. These 2000 unique SNP sensor beads self assemble in each bundle of 50,000 fibers to create an array with an approximately twenty-five-fold redundancy. This built-in

illumina
making sense out of life

redundancy improves the reliability and accuracy of the results generated by the BeadArray technology.

Illumina further fabricates its BeadArray bundles into a matrixed device, which we call our Array of Arrays™ platform, where each fiber bundle of the larger array matches a well of a standard microtiter plate. In the 96 well configuration and at 2000 bead types per array bundle, this Array of Arrays format would enable up to 192,000 individual genotypes to be scored in parallel.

Built-In Quality Control

Following array assembly and as a component of our manufacturing process, we deploy a proprietary decoding process to determine which bead type resides in which fiber core. Beyond generating a map that is used in downstream analytical work, our decoding process delivers inherent quality control as it validates the performance of each bead on each array.

With our Oligator™ custom DNA synthesis technology, Illumina also manufactures the oligonucleotides used in our BeadArray products, thus controlling the quality and supply of the oligonucleotides used in our BeadArray products and in SNP genotyping services.

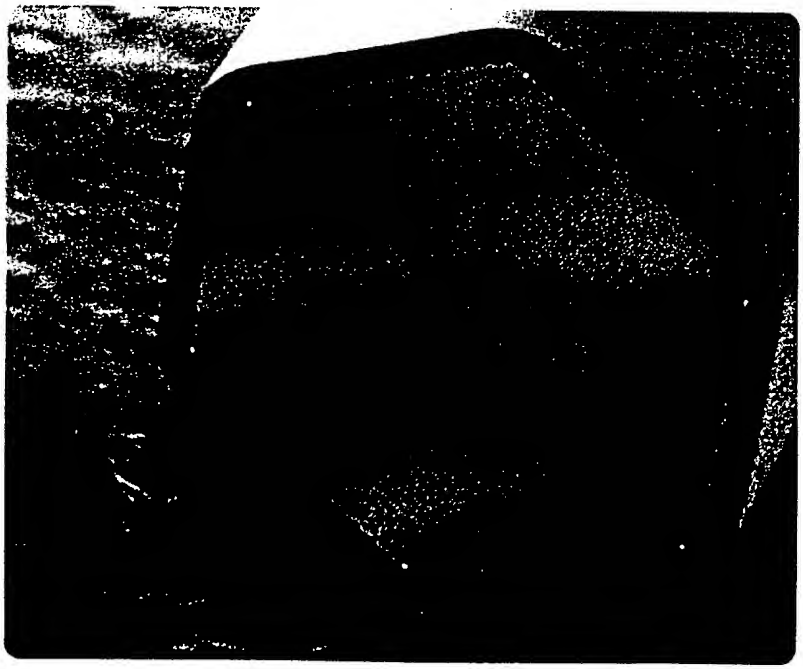
KEY ADVANTAGES OF ILLUMINA'S TECHNOLOGY

Throughput: Miniaturization, multiplexing and automation drive throughput.

Cost Effectiveness: Proprietary manufacturing process provides low cost structure.

Accuracy: Decoding performs a quality control step for every feature on every array. Redundancy provides robustness and improves data quality.

Flexibility: Various shapes, sizes and configurations of fiber bundles with choices of bead chemistry results in a flexible platform.



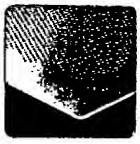
Illumina's initial BeadArray implementation contains approximately 50,000 beads in individual 3-micron wells at the end of each fiber strand.

BeadArray Technology
How it works

❶ Compatible with manual or robotic operation, our Array of Arrays format is designed to match the wells of standard microtiter plates.

❷ Close up of the bead-containing ends of the fiber bundles arrayed in a 96-well format.

❸ Dipping the fiber optic bundle into a chemical solution etches a microscopic well at the end of each individual fiber in the bundle.



❹ To form an array, we dip each fiber bundle into a pool of coated beads which self-assemble into the wells, one bead per well.

❺ Up to 2000 different bead types, with each bead type containing oligonucleotides of a unique sequence, can be represented in each bundle, with a targeted twenty five-fold average redundancy per bead type.

ARTIST'S RENDERING

❻ Hundreds of thousands of molecules of the same type coat each bead. We determine which bead type occupies which well via a proprietary decoding process.

ARTIST'S RENDERING

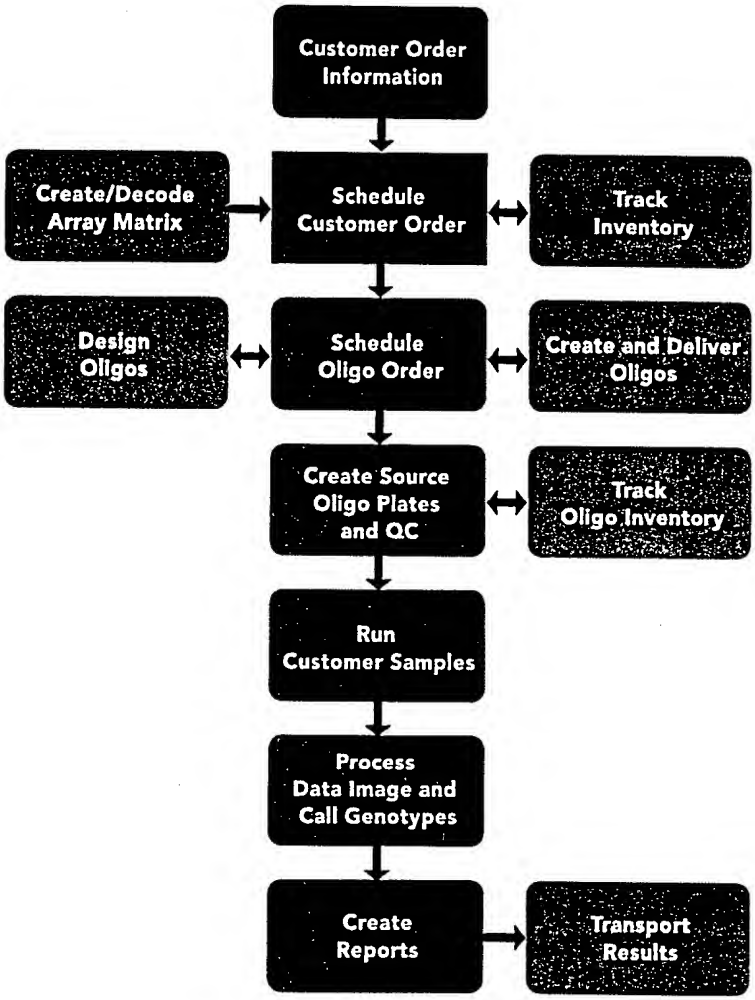
❼ The molecules in the sample hybridize, or bind to their complementary molecules on the coated bead.

LIMS ENVIRONMENT

Illumina has enabled its BeadArray technology with a state-of-the-art laboratory information management system (LIMS) to create an ultra-high-throughput genotyping service operation.

The LIMS environment was created as a customized database system for the workflow tracking and management in our genotyping facility. Every sample is given a unique identifier in the LIMS that links the genotyping order with specific reagents, microtiter plates and oligos. This allows the LIMS database to actively monitor all operations and ensure error free sample processing.

Our genotyping facility is designed to grow with customer needs and business demands. We have modularized our automated system to eliminate bottlenecks without sacrificing flexibility and cost. If more upfront sample processing is required, we simply install additional sample processing modules without affecting any downstream genotyping processes. This allows us to scale effortlessly while maintaining the strict rigor of sample handling and control.

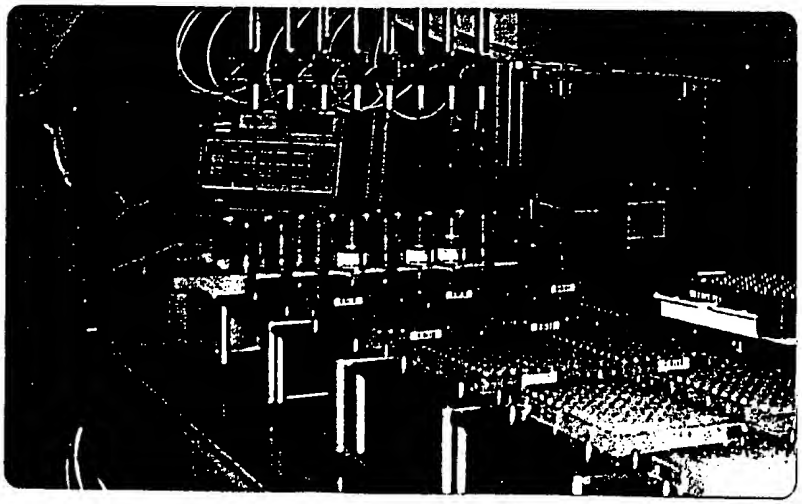


Simplified flow diagram of Illumina's SNP genotyping service, which is automated and LIMS-enabled at every step of the process.

HOW WE WORK WITH YOU

Illumina has assembled an experienced team of scientific professionals to deploy BeadArray technology in an automated, LIMS-controlled production environment. We take a highly collaborative approach to our customer relationships, maintaining strict confidentiality while pursuing ongoing dialogue to ensure productive results.

To get started, we will first test samples of your anonymized DNA for assay compatibility prior to the initiation of a genotyping project.



We will then provide you with bar-coded plates for shipment of samples to Illumina, followed up by quality-control checks on each sample. Only then will we begin the study. The amount of genomic DNA required by a study will be determined by the number of SNP loci analyzed for each sample. To calculate the amount of genomic DNA required for a sample, please contact Illumina or see our Frequently Asked Questions brochure available on our website.

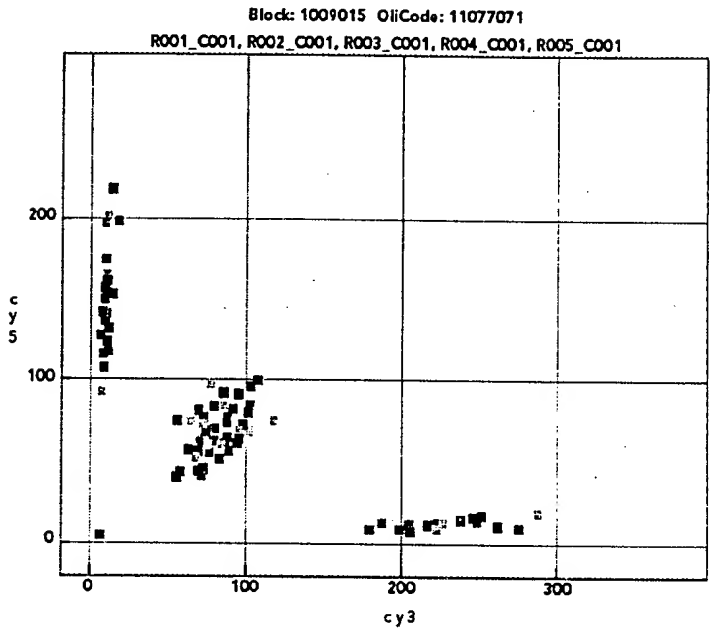
For your study, we encourage a collaborative approach to designing the study and selecting the SNP loci. We can validate the loci for you and will convert those loci into functional assays.

ACCURACY (STRAND CORRELATION)*

Study Set	% Accuracy
1	98.9
2	99.3
3	99.4
4	99.7

*This chart represents results generated from four sets of Loci (approximately 100 loci in each set) from 55,912 Alleles at a 90% call rate.

GENOTYPING CLUSTERING:
1 LOCUS FROM A 96 MULTIPLEXED LOCI SET WITH 96 DNA SAMPLES



MORE INFORMATION

To learn more about Illumina's SNP genotyping services, BeadArray technology, Oligator custom DNA synthesis services, or other products and services, please visit our website or contact us at the address below.

Note: Please visit our website for the most recent version of this document.

Illumina, Inc.
9885 Towne Centre Drive
San Diego, CA 92121-1975
tel 1.858.202.4500
fax 1.858.202.4545
www.illumina.com

illumina™ making sense out of life

Enter the New World

Welcome to the new world. A world where genotyping studies can be conducted with speed, sample throughput, and scale never before possible. At a lower cost than you ever imagined. Large studies that once took years can now be completed in months or even days.

With a throughput level of 1,000,000 calls per day, Illumina's SNP genotyping service leverages our proprietary BeadArray™ technology. The BeadArray platform will be available as a product later this year, but you can access its remarkable benefits now through our new genotyping service.

Illumina's service operation integrates a high degree of automation with advanced LIMS to manage linkage analyses, fine chromosomal mapping, candidate gene and large association studies.

So expand your expectations. Readjust your planning calendar. And join us in the new world of genotyping.

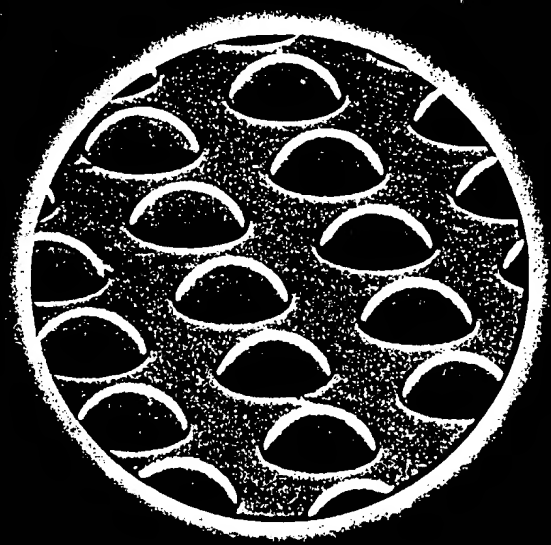
Learn more by calling us at **1.800.809.4566** or visiting **www.illumina.com/1snp**

Illumina's 96-bundle SentrixⓇ Array allows parallel processing of over 150,000 SNPs.

illumina.
making sense out of life


illumina

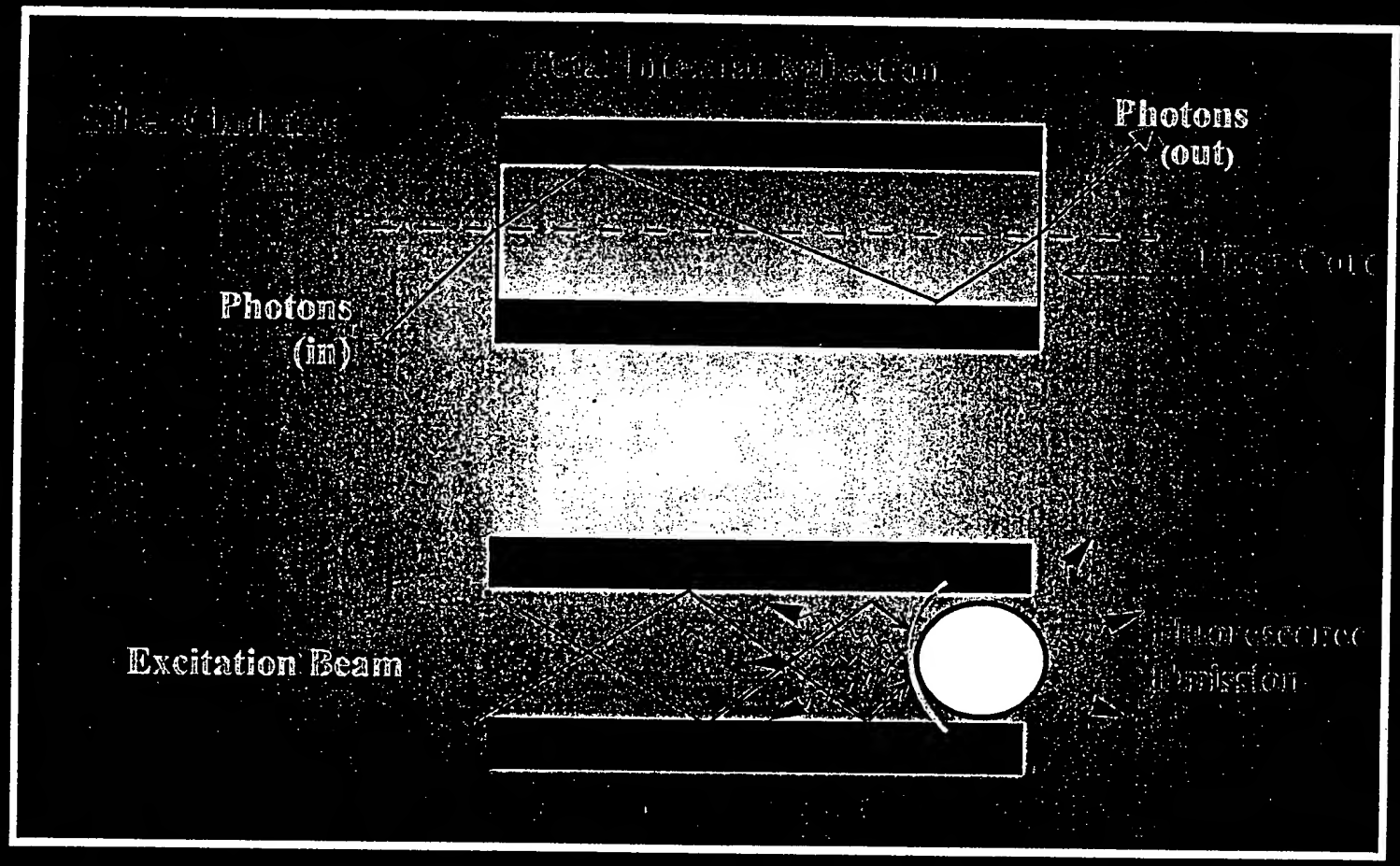
Illumina's Revolutionary Technology: Bringing Fiber Optics to Biology



- Throughput
- Cost-effectiveness
- Accuracy
- Flexibility

illumina

Bringing Fiber Optics to Biology



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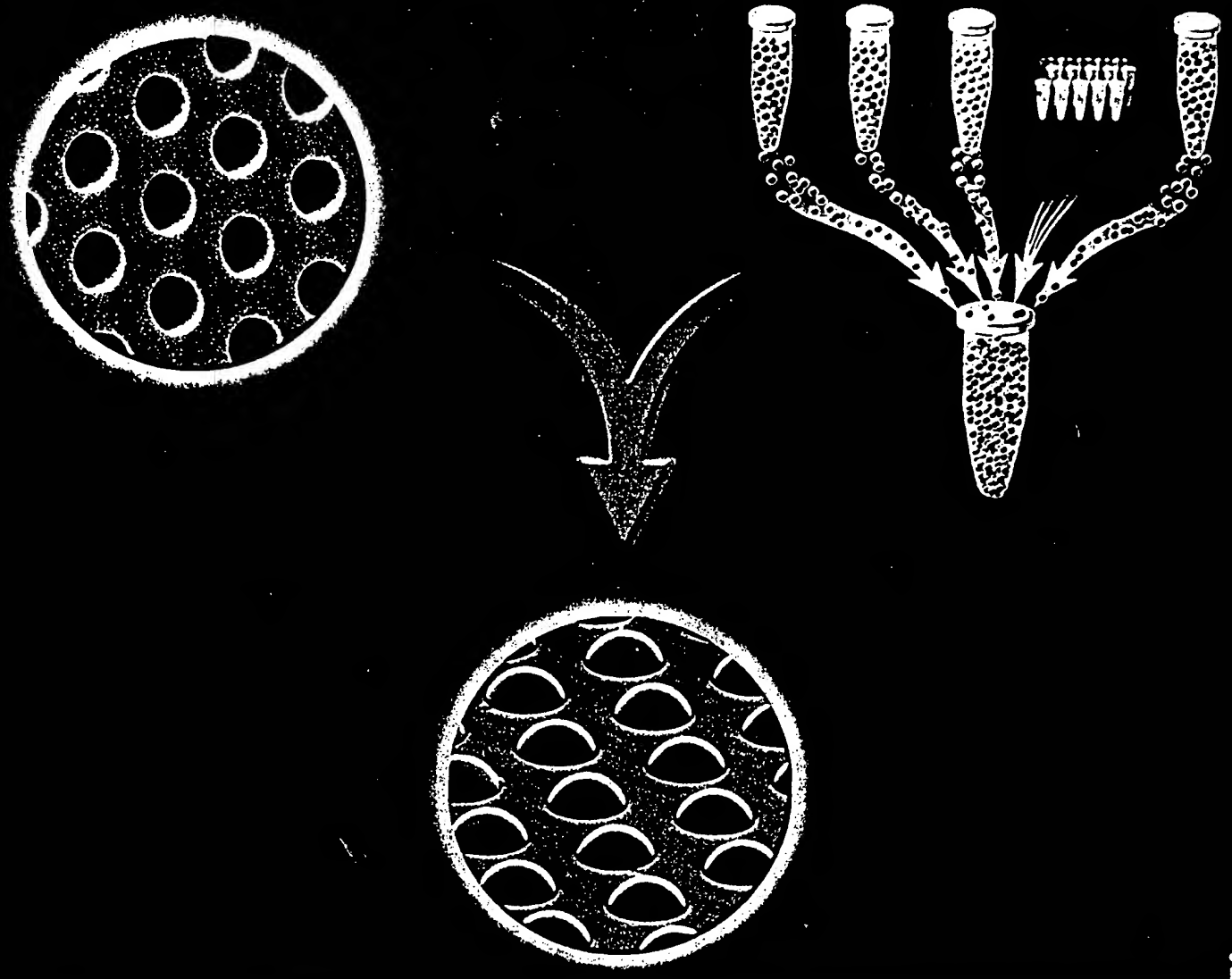
The BeadArray™ Assembly Process



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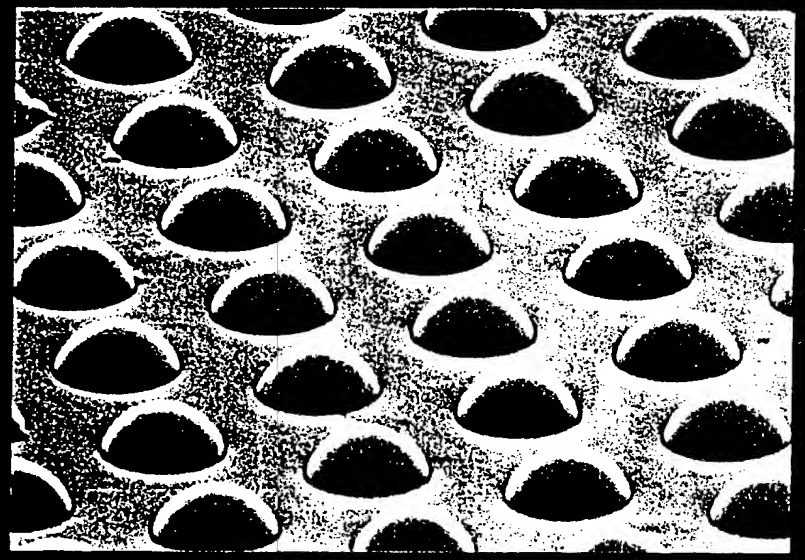
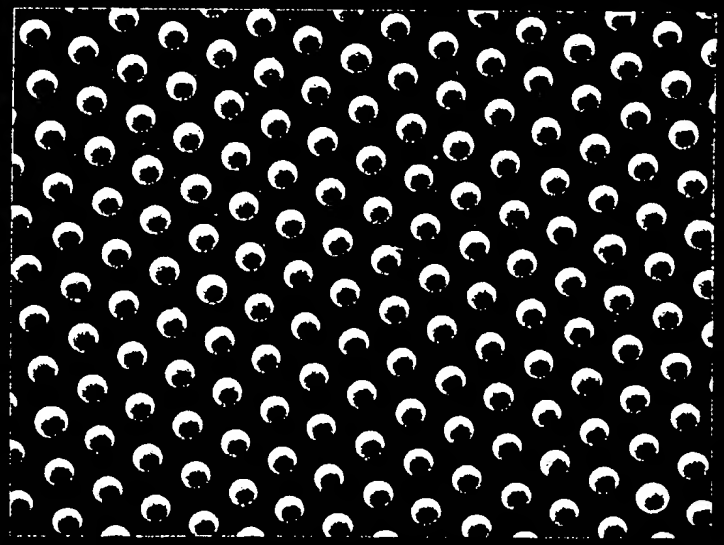
"Optically Wired" Beads in Wells





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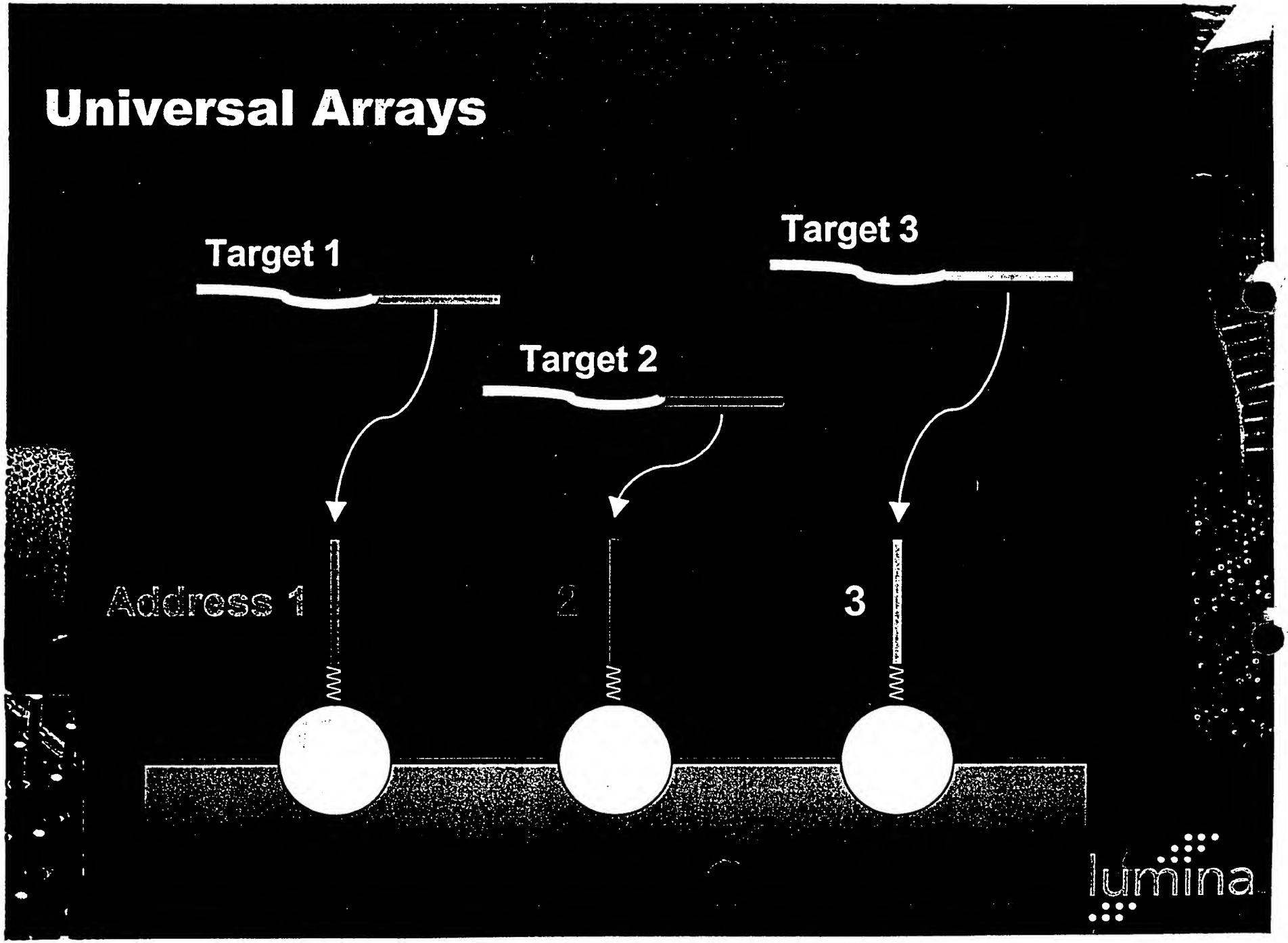
Universal Arrays



Random Bead Arrays Require Decoding

- Standard arrays are "ordered"
  - Each element is manufactured in a known place
    - Robotic spotting
    - Photolithography
    - Ink jet synthesis
- Illumina Bead Arrays are "random"
  - Manufactured by self-assembly
  - Beads are identified by decoding

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Optimization of the Assay

Ligation	- Buffer composition - Temperature, Time - Enzyme concentration - Concentrations of gDNA, oligos
PCR Amplification	- Primer sequences - Cycle Profile - Uniformity
Hybridization to Array	- Buffer composition - ss-DNA vs. ds-DNA
Imaging	- Buffer composition - Equipment, Software

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Some Dimensions of Genotyping

- Assay
- **Production System**
- Quality metrics/Controls
- DNAs
- Loci
- Production/Data
- Summary/Plans/Capacity

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Genotyping Service Facility

Resources

- 5 Tecan Robots
- 5 People
- 3 Thermal Cyclers
- 4 Ovens
- 2 Array Readers

Capacity

- ~1,000,000 Genotypes / Day

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Automation Principles

- Custom LIMS Design
  - Fail-safe sample tracking
  - Experience with clinical sample tracking
- Modular robotics
  - Scalable
  - Fast Development Time
- Coordination with assay development
  - A common language for defining processes

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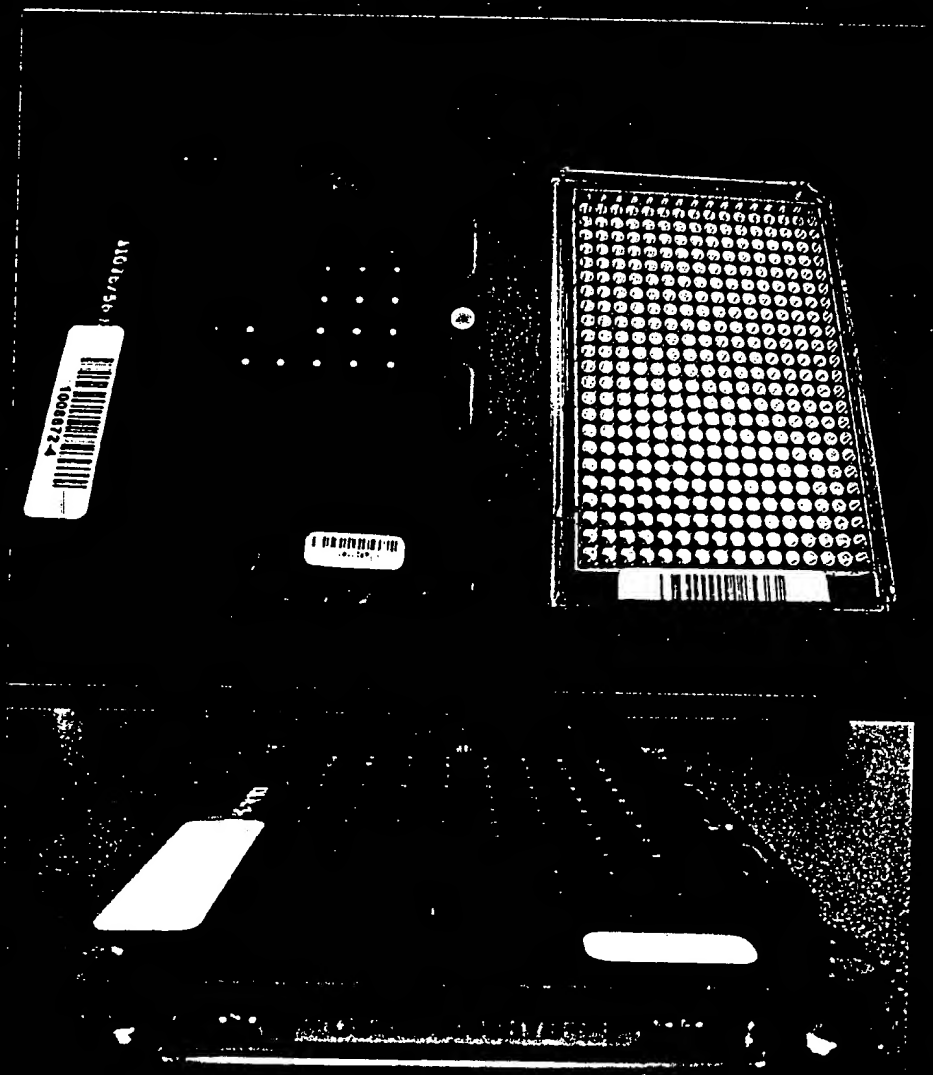
Hybridization



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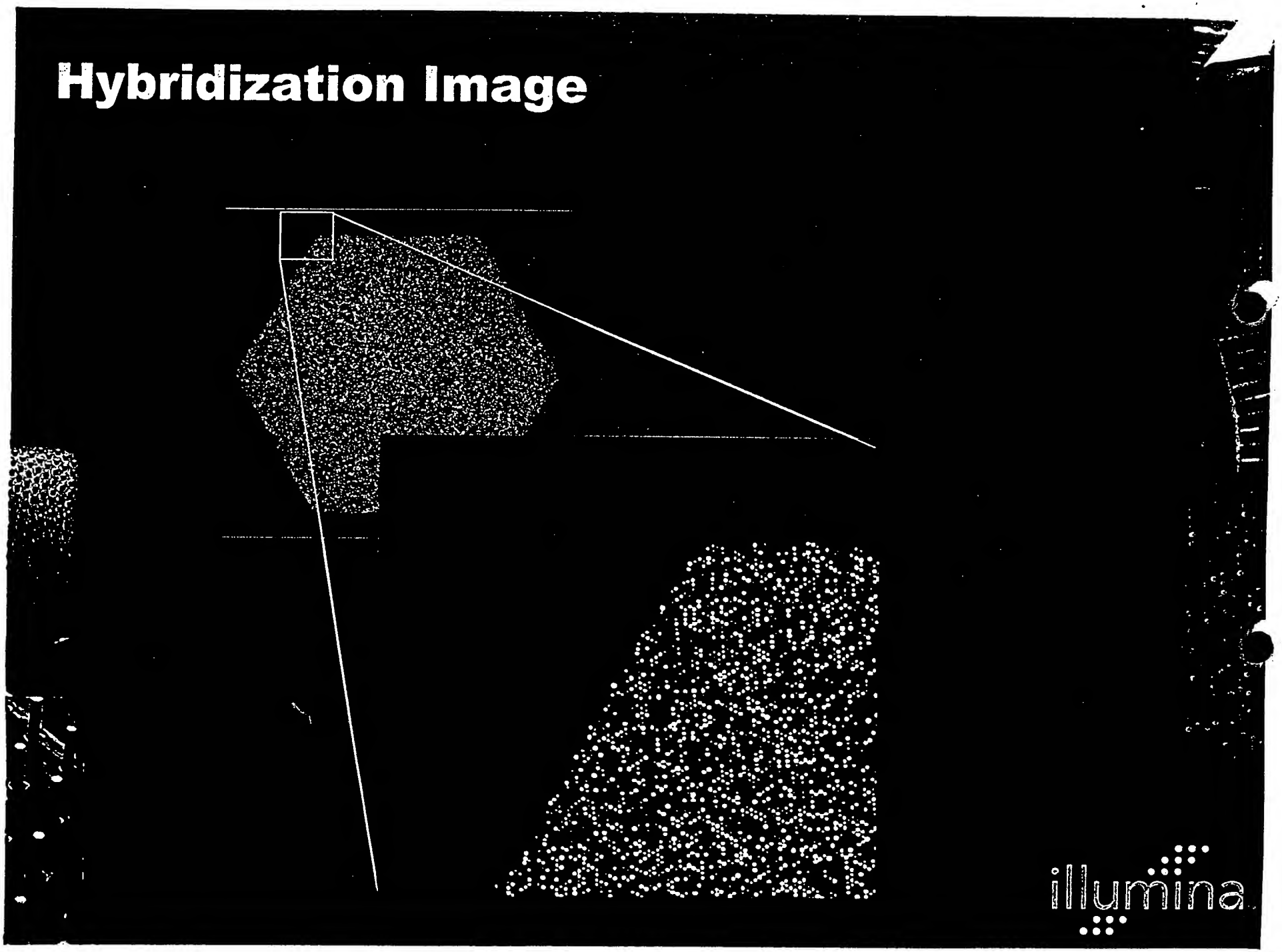
Hybridization Image



Some Dimensions of Genotyping

- Assay
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Some Dimensions of Genotyping

- Assay
- Production System
- Quality metrics/Controls
- **DNAs / Loci**
- Production/Data
- Summary/Plans/Capacity

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Locus Development Success Factors

- Allele frequency & source of allelic DNA
- Repeated sequences around polymorphism
- Palindromic sequences
- GC & AT rich sequences
- Neighboring polymorphisms
- Reagent variables (oligos)

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Estimates of Accuracy

- Strand Correlation
  - Loci developed on both strands
  - Assumes strand independence in locus development
- Reproducibility
  - Duplicated DNAs
  - Assumes equivalence of DNAs

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Array Readers

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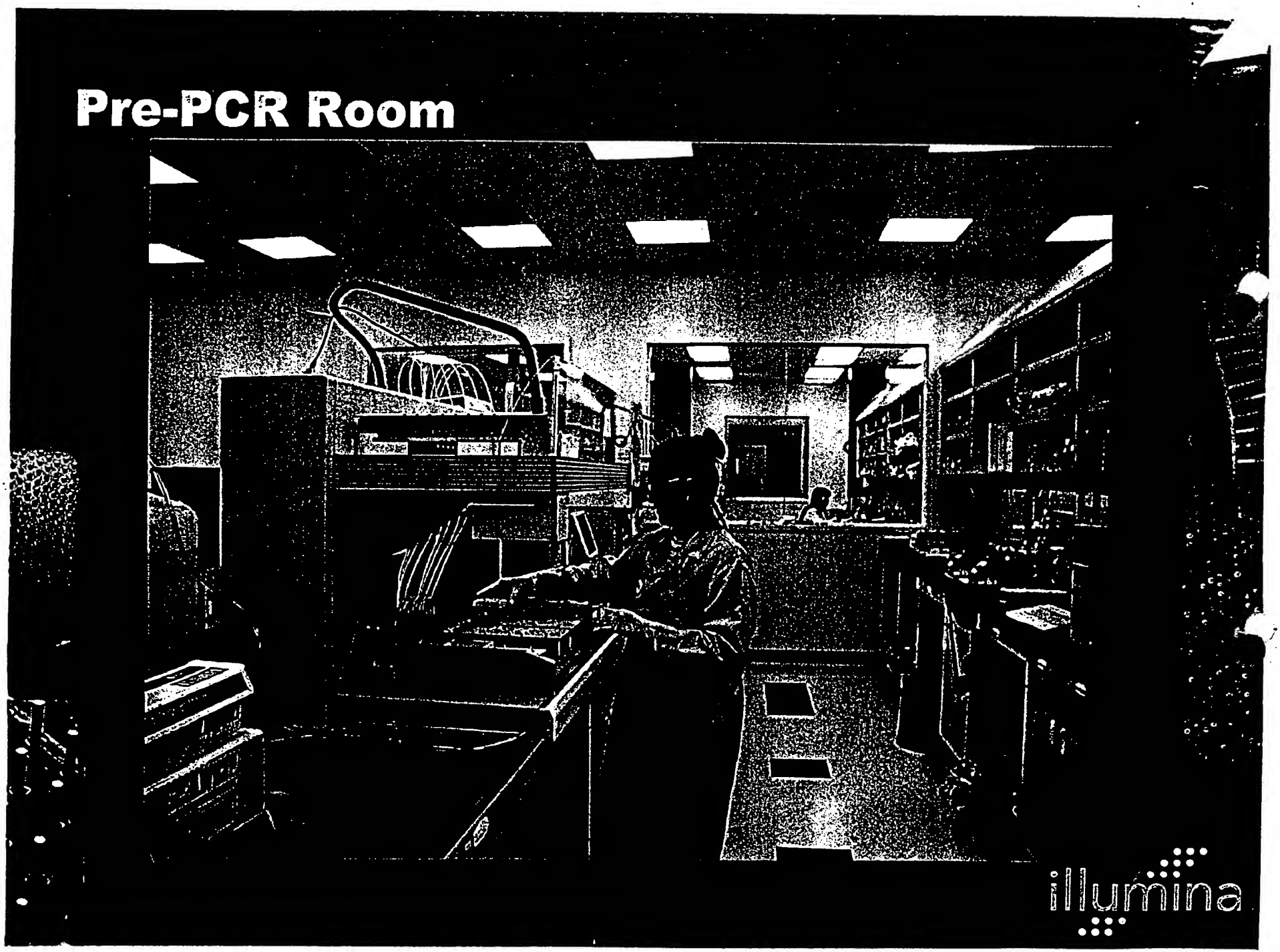
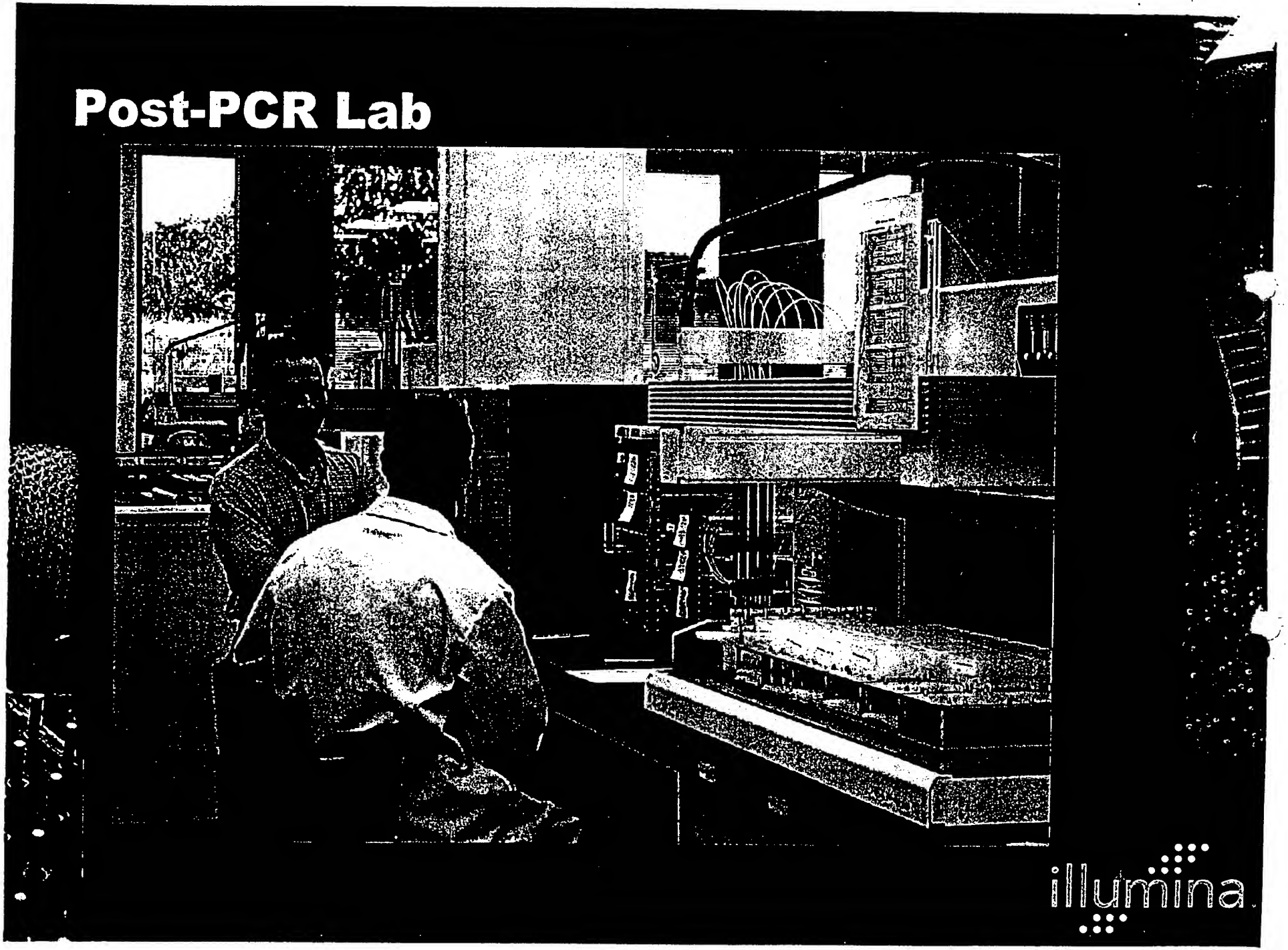
Pre-PCR Room



Post-PCR Lab



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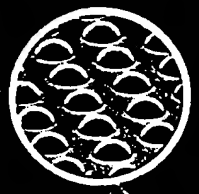
Commercialization Model

Technology	Platforms	Applications

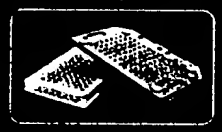
BeadArray™



Oligator™

1536-Well

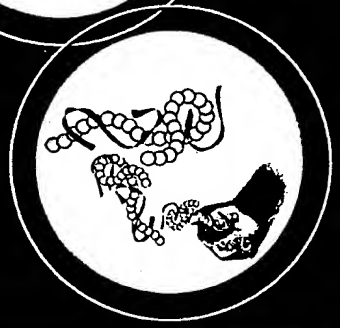
384-Well



96-Well

SNP Genotyping

Expression Profiling



Proteomics

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Some Dimensions of Genotyping

- Assay
- Production System
- Quality metrics/Controls
- DNAs
- Loci
- **Production/Data**
- Summary/Plan Capacity

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Commercialization Model

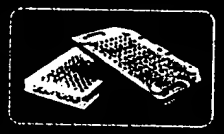
Technology	Platforms	Applications

BeadArray™

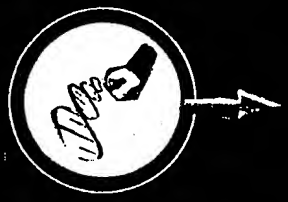
Oligator™

1536-Well

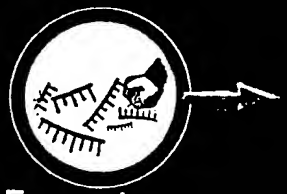
384-Well



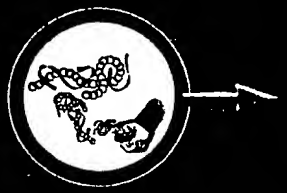
96-Well



SNP Genotyping



Expression Profiling



Proteomics

Assay Development

Custom Assays
- "Customer Favorites"
- 100-1000 SNPs

Linkage
- Candidate Genes
- 1K-5K SNPs

Linkage Disequilibrium
- Whole-Genome Scans
- 100K-200K SNPs

Focused Sets
- 1K-10K Genes
- Lots of Samples

Whole Genomes

Antibodies

Alternative Capture Molecules

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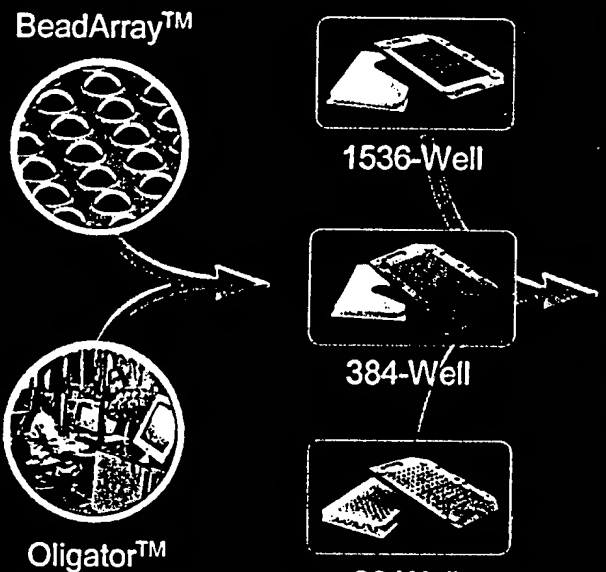
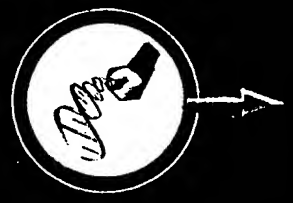
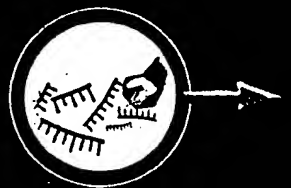
Commercialization Model

Technology	Platforms	Applications	Assay Development	Commercialization




SNP Genotyping


Expression Profiling


Proteomics

- Custom Assays
- Linkage
- Linkage Disequilibrium

- Focused Sets
- Whole Genomes

- Antibodies
- Alternative Capture Molecules

Services: Oligos

Products: ABI Partnership

Direct Sales

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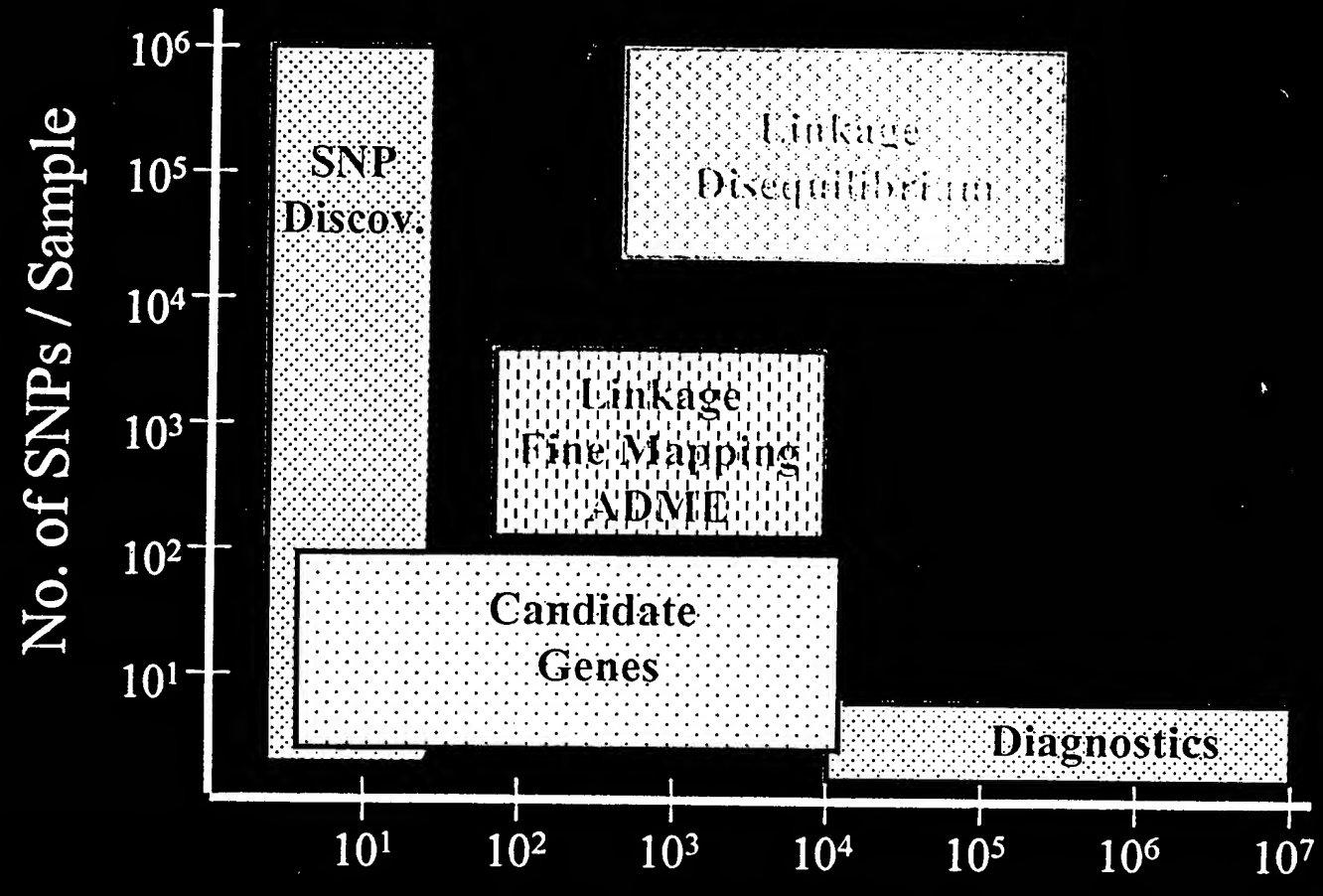
SNP Market Segmentation



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Some Dimensions of Genotyping

- Assay
- Production System
- Quality metrics/Controls
- DNAs
- Loci
- Production/Data
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Fiber Bundles: A Flexible Platform

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Illumina's Technology Advantages

- **Throughput:** Miniaturization yields greater informational density than any other format and product formats are compatible with conventional automation.
- **Cost-effectiveness:** Proprietary manufacturing process provides low cost structure.
- **Accuracy:** Decoding performs a quality control step for every feature on every array and multiple bead types improves data quality.
- **Flexibility:** Various shapes, sizes and configurations of fiber bundles with choices of bead chemistry results in a flexible platform.

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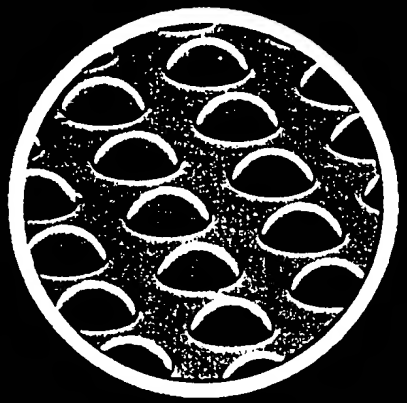
Commercialization Model

Technology | [illegible] | Applications | Assay Development | Commercialization



BeadArray™

Oligator™

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news releases

Illumina Signs Genotyping Services Agreement With Johns Hopkins Medical University

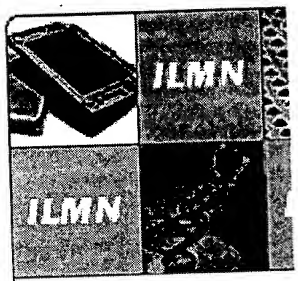
SNP Scoring Service to Leverage Illumina's BeadArray (TM) Platform Technology

SAN DIEGO, CALIFORNIA, January 8, 2002 -- Illumina, Inc. announced today that it has signed a commercial agreement with Johns Hopkins Medical University, Institute of Genetic Medicine to provide single nucleotide polymorphism (SNP) genotyping services on a sample collection provided by the Institute. Under the terms of the agreement, Illumina will use its BeadArray technology to "score," or determine the frequency of specified SNPs in the sample set. Illumina will also design functional assays for most of the SNP loci provided by the Institute. Further details about the agreement were not disclosed.

"Johns Hopkins is a world leader in the research of genetic factors associated with conditions such as cleft lip and palate and isolated craniosynostosis, and we're pleased to be able to directly support their groundbreaking research activities," stated Jay Flatley, Illumina President and CEO. "Our genotyping service capacity has reached one million genotypes per day in a highly multiplexed environment, and we look forward to working collaboratively with Johns Hopkins and other organizations to speed the analysis and lower the cost of large genotyping studies."

Illumina (Nasdaq: ILMN; www.illumina.com) is developing next-generation tools that will permit large-scale analysis of genetic variation and function. The Company's proprietary BeadArrayÔ technology will provide the throughput, cost effectiveness and flexibility necessary to enable researchers in the life sciences and pharmaceutical industries to perform the billions of tests necessary to extract medically valuable information from advances in genomics. Illumina's technology will have applicability across a wide variety of industries beyond life sciences and pharmaceuticals, including agriculture, food, chemicals and petrochemicals.

Statements included in this press release that are not



Illumina's BeadArray™ platfor high throughput, flexibility and

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Latest news and operating results

We've formed some key alliances

Learn more about our technology platform

historical in nature may be "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of such forward-looking statements include statements about Illumina's product introduction timeline or the Company's ability to further commercialize its genetic analysis services business or develop its core technologies. Any such forward-looking statements involve risks and uncertainties and reflect Illumina's judgment as of the date of this release. Actual events or results may differ from Illumina's expectations as a result of risks and uncertainties identified from time to time in the Company's reports filed with the U.S. Securities and Exchange Commission, including those discussed in "Factors Affecting Our Operating Results" and elsewhere in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000 or in information disclosed in public conference calls, the date and time o which are released beforehand. Illumina disclaims any intent or obligation to update these forward-looking statements beyond the date of this release and claims the protection of the Safe Harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

###

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news releases

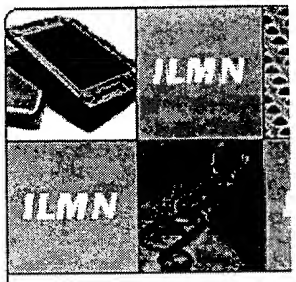
Illumina Signs Genotyping Services Agreement with Investigators at Boston University

SNP Scoring Service to Leverage Illumina's BeadArray (TM) Platform Technology

SAN DIEGO, CALIFORNIA, January 28, 2002 -- Illumina, Inc. announced today that it has signed a commercial agreement with investigators at Boston University Medical Center to provide single nucleotide polymorphism (SNP) genotyping services for a large-scale research project on preterm birth. Under the terms of the agreement, Illumina will use its BeadArray (TM) technology to "score" a set of SNPs thought to be associated with preterm birth. Illumina will also design SNP assays for the SNP loci provided by the investigators. Further details about the agreement were not disclosed.

"We are pleased that investigators at Boston University Medical Center have decided to leverage the power and cost-effectiveness of our BeadArray technology," stated Jay Flatley, Illumina President and CEO. "Investigators at Boston University Medical Center are conducting leading-edge research to understand environmental and genetic determinants of preterm birth, which is the leading cause of infant mortality and morbidity," continued Flatley. "We look forward to continued collaborations with investigators at Boston University Medical Center and other organizations to speed the analysis and lower the cost of genotyping."

Illumina (Nasdaq: ILMN; www.illumina.com) is developing next-generation tools that will permit large-scale analysis of genetic variation and function. The Company's proprietary BeadArray technology will provide the throughput, cost effectiveness and flexibility necessary to enable researchers in the life sciences and pharmaceutical industries to perform the billions of tests necessary to extract medically valuable information from advances in genomics. Illumina's technology will have applicability across a wide variety of industries beyond life sciences and pharmaceuticals, including agriculture, food, chemicals and petrochemicals.



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news releases

Illumina Signs Genotyping Services Agreement with GlaxoSmithKline

SNP Scoring Service to Leverage Illumina's BeadArray Platform Technology

SAN DIEGO, CALIFORNIA, June 29, 2001 -- Illumina, Inc. announced today that it has signed a commercial agreement with GlaxoSmithKline (GSK) to provide single nucleotide polymorphism (SNP) genotyping services on a sample collection provided by GSK. Under the terms of the agreement, Illumina will use its BeadArray technology to "score," or determine the frequency of specified SNPs in the sample set. Further details were not disclosed.

"We're pleased to begin working with GlaxoSmithKline, a global pharmaceutical firm and leader in employing new technologies to accelerate drug discovery," stated Jay Flatley, Illumina President and CEO. "Commercialization of our genetic analysis services business will drive the scale-up of genotyping assay development and help us refine BeadArray core technologies," added Flatley.

Illumina (Nasdaq: ILMN; www.illumina.com) is developing next-generation tools that will permit large-scale analysis of genetic variation and function. The Company's proprietary BeadArrayÔ technology will provide the throughput, cost effectiveness and flexibility necessary to enable researchers in the life sciences and pharmaceutical industries to perform the billions of tests necessary to extract medically valuable information from advances in genomics. Illumina's technology will have applicability across a wide variety of industries beyond life sciences and pharmaceuticals, including agriculture, food, chemicals and petrochemicals.

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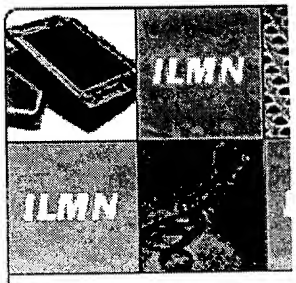

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develop its core technologies. Any such forward-looking statements involve risks and uncertainties and reflect Illumina's judgment as of the date of this release. Actual events or results may differ from Illumina's expectations as a result of risks and uncertainties identified from time to time in the Company's reports filed with the U.S. Securities and Exchange Commission, including those discussed in "Factors Affecting Our Operating Results" and elsewhere in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000 or in information disclosed in public conference calls, the date and time o which are released beforehand. Illumina disclaims any intent or obligation to update these forward-looking statements beyond the date of this release and claims the protection of the Safe Harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

Press Release

03/OX/02
19th March 2002

ILLUMINA AND OXAGEN TO COLLABORATE ON FINE MAPPING OF SNP LOCI IN GENETIC LINKAGE REGIONS

Illumina's BeadArray™ Technology to Enable Detailed Exploration of Linkage Regions;
Oxagen to Add Potential New Targets to Discovery Pipeline

SAN DIEGO, CALIFORNIA (USA) and ABINGDON, ENGLAND- March 19, 2002 - Illumina, Inc. (Nasdaq: ILMN) and Oxagen Limited, a private clinical genomics company, announced today that they have signed a collaborative, commercial agreement to generate detailed maps of single nucleotide polymorphism (SNP) clusters in defined chromosomal regions. Under the terms of the agreement, Oxagen will provide a collection of SNP loci within linkage regions together with samples from their extensive library of family collection material and information. Illumina will use its BeadArray technology to design functional assays for the SNPs provided and generate several million overall genotype calls from the sample set. Oxagen will retain rights to all genes and novel associations discovered as a result of the study. Further details about the agreement were not disclosed.

Jay Flatley, Illumina President & Chief Executive Officer, noted "Oxagen is taking a systematic, genome-wide approach to understanding the molecular basis of disease. Dr Nicholls and his team have built a large, proprietary collection of family samples and data, which represent a powerful resource for identifying and validating disease-causing genes. We're looking forward to our relationship with Oxagen, and we're confident that our genotyping capability will provide valuable information that paves the way for the identification of disease genes."

Dr. Trevor Nicholls, Oxagen Chief Executive Officer, commented "Oxagen has now created an exceptionally strong base of knowledge in relation to linkage regions relevant to the diseases we are studying. Illumina's BeadArray platform will give us the sample throughput and accuracy we need to extract the maximum information from our valuable samples. Equally important, Illumina's technology is driving down genotyping costs and making feasible large-scale studies like this one. We're very pleased about our collaboration with Illumina and expect that it will allow Oxagen to accelerate its development of improved therapeutic approaches and diagnostic tests."

Notes To Editors

About Illumina
Illumina (www.illumina.com) is developing next-generation tools that permit large-scale analysis of genetic variation and function. The Company's proprietary BeadArray™ technology provides the throughput, cost effectiveness and flexibility necessary to enable researchers in the life sciences and pharmaceutical industries to perform the billions of tests necessary to extract medically valuable information from advances in genomics. Illumina's technology will have applicability across a wide variety of industries beyond life sciences and pharmaceuticals, including agriculture, food, chemicals and petrochemicals.

About Oxagen
Oxagen (www.oxagen.co.uk) has rapidly established itself as a leading player in the study of complex disease genetics, conducting programs in cardiovascular disease, inflammatory

disease and metabolic and endocrine disorders. Oxagen aims to identify new therapeutics and diagnostics by capitalizing on insights from genetics and specializes in using large-scale family studies to understand the association of genes and genetic variations with disease. The Company believes that this approach is the most effective way to provide fundamental insights into the molecular mechanisms of disease. To this end, Oxagen is building its capabilities in functional biology to take forward these discoveries, on its own account and in partnership with major pharmaceutical companies.

Statements included in this press release that are not historical in nature may be "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of such forward-looking statements include statements about Illumina's ability to deploy its genotyping services business for large-scale studies. Any such forward-looking statements involve risks and uncertainties and reflect Illumina's judgment as of the date of this release. Actual events or results may differ from Illumina's expectations as a result of risks and uncertainties identified from time to time in the Company's reports filed with the U.S. Securities and Exchange Commission, including those discussed in ``Factors Affecting Our Operating Results" and elsewhere in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000 or in information disclosed in public conference calls, the date and time of which are released beforehand. Illumina disclaims any intent or obligation to update these forward-looking statements beyond the date of this release and claims the protection of the Safe Harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

For further information contact:

Illumina

Jay Flatley, President & Chief Executive Officer — Tel: +1 858 202 4501

William Craumer, Marketing Communications Director — Tel: +1 858 202 4667

Oxagen Limited

Dr. Trevor Nicholls, Chief Executive Officer — Tel: +44 (0)1235 443300

Ms Christine Soden, Chief Financial Officer

Trade/Scientific Press Enquiries

HCC De Facto Group,
Dr Chris Gardner, Associate Director — Tel: +44 (0)20 7496 3300

Glossary Links

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news releases

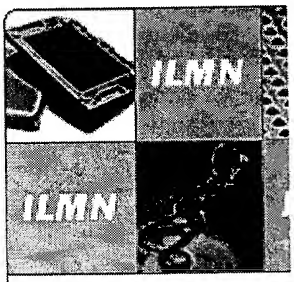
Illumina Signs Genotyping Services Agreement with University of California, San Diego and San Diego VA Healthcare System

BeadArray(TM) Technology To Help Correlate SNP Genotypes with Bipolar Psychiatric Disorders

SAN DIEGO, CALIFORNIA, April 25, 2002 -- Illumina, Inc. announced today that it has signed a commercial agreement with the University of California, San Diego (UCSD), to provide single nucleotide polymorphism (SNP) genotyping services on a sample collection provided by the University's Laboratory of Psychiatric Genomics. Under the terms of the agreement, Illumina will use its BeadArray technology to genotype specified SNPs in the sample set. Illumina will also identify potential SNPs for the study and design functional assays for the SNP loci, many of which are located on chromosome 22 and believed to be associated with bipolar disorders and schizophrenia. The study will be funded by a grant from the Department o Veterans Affairs. Further details about the agreement were not disclosed.

Jay Flatley, Illumina President & CEO, noted "UCSD is increasingly at the forefront of groundbreaking research in the field of psychiatry. We're very pleased to work with UCSD on this study, the results of which may provide a better understanding of the genetic basis of bipolar psychiatric disorders and suggest a clearer path for therapeutic development and improved patient outcomes. We're also excited to see further deployment of BeadArray technology in our services operation."

Illumina (Nasdaq: ILMN; www.illumina.com) is developing next-generation tools that permit large-scale analysis o genetic variation and function. The Company's proprietary BeadArrayÔ technology provides the throughput, cos effectiveness and flexibility necessary to enable researchers in the life sciences and pharmaceutical industries to perform the billions of tests necessary to extract medically valuable information from advances in genomics and proteomics. Illumina's technology will have applicability across a wide variety of industries beyond life sciences and pharmaceuticals, including agriculture, food,



Illumina's BeadArray™ platfor high throughput, flexibility and

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chemicals and petrochemicals.

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###

illumina™ making sense out of life

news releases

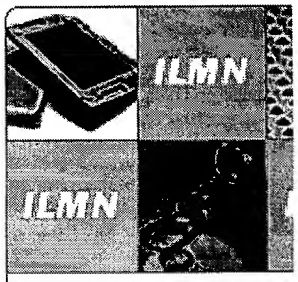
Illumina and Oxagen to Collaborate on Fine Mapping of SNP Loci in Genetic Linkage Regions

Illumina's BeadArray(TM) Technology to Enable Detailed Exploration of Linkage Regions; Oxagen to Add Potential New Targets to Discovery Pipeline

SAN DIEGO, CALIFORNIA (USA) and ABINGDON, ENGLAND, March 19, 2002 - Illumina, Inc. (Nasdaq: ILMN) and Oxagen Limited, a private clinical genomics company, announced today that they have signed a collaborative, commercial agreement to generate detailed maps of single nucleotide polymorphism (SNP) clusters in defined chromosomal regions. Under the terms of the agreement, Oxagen will provide a collection of SNP loci within linkage regions together with samples from their extensive library of family collection material and information. Illumina will use its BeadArray technology to design functional assays for the SNPs provided and generate several million overall genotype calls from the sample set. Oxagen will retain rights to all genes and novel associations discovered as a result of the study. Further details about the agreement were not disclosed.

Jay Flatley, Illumina President & Chief Executive Officer, noted "Oxagen is taking a systematic, genome-wide approach to understanding the molecular basis of disease. Dr Nicholls and his team have built a large, proprietary collection of family samples and data, which represent a powerful resource for identifying and validating disease causing genes. We're looking forward to our relationship with Oxagen, and we're confident that our genotyping capability will provide valuable information that paves the way for the identification of disease genes."

Dr. Trevor Nicholls, Oxagen Chief Executive Officer, commented "Oxagen has now created an exceptionally strong base of knowledge in relation to linkage regions relevant to the diseases we are studying. Illumina's BeadArray platform will give us the sample throughput and accuracy we need to extract the maximum information from our valuable samples. Equally important, Illumina's technology is driving down genotyping costs and making



Illumina's BeadArray™ platfor
high throughput, flexibility and

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feasible large-scale studies like this one. We're very pleased about our collaboration with Illumina and expect that it will allow Oxagen to accelerate its development o improved therapeutic approaches and diagnostic tests."

About Illumina Illumina (www.illumina.com) is developing next-generation tools that permit large-scale analysis o genetic variation and function. The Company's proprietary BeadArray(TM) technology provides the throughput, cost effectiveness and flexibility necessary to enable researchers in the life sciences and pharmaceutical industries to perform the billions of tests necessary to extract medically valuable information from advances in genomics. Illumina's technology will have applicability across a wide variety of industries beyond life sciences and pharmaceuticals, including agriculture, food, chemicals and petrochemicals.

About Oxagen Oxagen (www.oxagen.co.uk) has rapidly established itself as a leading player in the study o complex disease genetics, conducting programs in cardiovascular disease, inflammatory disease and metabolic and endocrine disorders. Oxagen aims to identify new therapeutics and diagnostics by capitalizing on insights from genetics and specializes in using large scale family studies to understand the association o genes and genetic variations with disease. The Company believes that this approach is the most effective way to provide fundamental insights into the molecular mechanisms of disease. To this end, Oxagen is building its capabilities in functional biology to take forward these discoveries, on its own account and in partnership with major pharmaceutical companies.

Statements included in this press release that are not historical in nature may be "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of such forward-looking statements include statements about Illumina's ability to deploy its genotyping services business for large-scale studies. Any such forward-looking statements involve risks and uncertainties and reflect Illumina's judgment as of the date of this release. Actual events or results may differ from Illumina's expectations as a result of risks and uncertainties identified from time to time in the Company's reports filed with the U.S. Securities and Exchange Commission, including those discussed in "Factors Affecting Our Operating Results" and elsewhere in the Company's Annual Report on Form 10-K for the fiscal yea ended December 31, 2000 or in information disclosed in public conference calls, the date and time of which are released beforehand. Illumina disclaims any intent or obligation to update these forward-looking statements beyond the date of this release and claims the protection of the Safe Harbor for forward-looking statement contained in the Private Securities Litigation Reform Act o 1995.

Illumina Contacts: Jay Flatley, President & Chief Executive Officer, +1.858.202.4501, jflatley@illumina.com or Willia Craumer, Marketing Communications Director,